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INTRODUCTION

Uses of Dosimetry in Radiation Epidemiology

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Radiation epidemiology seeks to describe and quantify the risk of health effects, often cancer, in populations exposed to ionizing and non-ionizing radiation. To do so, it is important to estimate organ or tissue doses for large numbers of exposed individuals with a moderate to high degree of certainty. Unlike dosimetry for establishing compliance with regulations, which relies on doses estimated for representative, maximally exposed, or highest-risk persons, dosimetry for analytical epidemiological studies usually requires developing new dosimetric models or tailoring existing ones to reach a higher level of individualization. The majority of radiation epidemiological studies conducted to date have required the reconstruction of dose to individuals or study populations that were exposed many years ago. This presents a major challenge to researchers, because measurements often are not available or do not exist in forms that are directly usable for calculating radiation doses on an individual basis. The goal of this special issue of *Radiation Research* is to introduce readers to an array of dosimetric methods and applications that have been developed to reconstruct radiation exposures for epidemiological studies. We intend to fill a void in the technical literature by describing these methods in terms understandable to epidemiologists, dosimetrists and statisticians so that these research tools can be used by other members of the research community.

This publication follows the 1995 National Academy of Sciences/National Research Council report entitled *Radiation Dose Reconstruction for Epidemiologic Uses* (*1*). That book summarized the views and expertise of a group of scientists who participated in a workshop on dose reconstruction for environmental radiation exposures. Since then, the methods for dose reconstruction have continued to advance, and the knowledge gained from epidemiological studies of populations exposed to radiation from many different sources has grown. It is therefore timely to publish a special issue of *Radiation Research* devoted to the methods used to estimate medical, occupational and environmental radiation doses to individuals within the context of epidemiological studies.

Radiation epidemiology studies can be classified by the circumstances of exposure, i.e. medical procedures, routine and accidental occupational exposures, or releases of radioactive materials to the environment, and we have grouped the papers in those categories. Most of the studies discussed in this issue have been conducted by, or in collaboration with, the Radiation Epidemiology Branch (REB) of the U.S. National Cancer Institute (NCI), and we think that they represent a cross section of epidemiological studies that have quantified radiation-related risks based on estimated individual doses. For example, in collaboration with investigators at the University of Texas M. D. Anderson Cancer Center, the Radiation Epidemiology Branch has a long history and extensive experience developing dosimetry methods for studies of populations exposed to radiation from medical procedures (*2*, *3*). Reconstruction of doses from radioactive fallout from nuclear testing (*4*–*8*) and accidents (*9*) has been an active area of research by REB for the past several years and has included the development of parameter values for environmental exposure models (*10*, *11*). REB also has been involved in using and evaluating dosimetric methods for estimating individual organ doses from exposure to radon and its radioactive decay products (*12*). Studies have incorporated estimates of radon concentration in homes using both contemporary (air monitors) (*13*) and retrospective (surface monitors on glass) measurements (*14*) to characterize radon exposure to individuals. Biodosimetry also can contribute important, independent estimates of radiation exposure. REB has incorporated several biological markers of radiation exposure in its studies (*15*–*21*). Finally, REB also has been investigating sources of uncertainty in dose estimates and has been active in the development of methods to account for uncertainty in dose–response analyses (*22*, *23*).

The dosimetry methods described in the papers in this issue have been applied to both external and internal sources of radiation, different levels of exposure, and radiation fields of varying uniformity and rates of delivery. Almost every study described in this issue has required unique methods to

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estimate radiation doses due to differences in the type and level of radiation exposure, the study population characteristics, and the variety and quality of available data.

Epidemiological studies of medical exposures to external sources of radiation for treatment of malignant and benign diseases have incorporated dosimetry methods to estimate organ doses inside as well as outside the treatment volume (*24, 25*). Radiation doses to specific organs have been estimated from laboratory measurements that simulate actual exposure situations using a combination of anthropomorphic and water phantoms, as well as numerical simulation models using mathematical phantoms (*3, 26*). Radiation doses from internal irradiation resulting from the use of radiopharmaceuticals for diagnostic or therapeutic purposes also are considered. A description of various methods for reconstructing medically related exposures is presented.

Occupational exposure to radiation is usually chronic and may be protracted over moderate to long periods. Studies of radiation workers provide an important source of information on the effects of exposure at low dose and low dose rates (*27*). Methods are discussed in this issue that have been used to estimate radiation exposure to various occupational groups including Chornobyl clean-up workers, miners exposed to radon, radiological technologists, and workers in the nuclear industries.

The reconstruction of doses from radioactive fallout from nuclear weapons testing and from other accidental environmental releases of radioactive materials has been an active area of dosimetry research for more than three decades. During that time, a variety of empirical and theoretical models has been developed to estimate radiation dose received from radiation external to the body as well as a consequence of ingesting or breathing contaminated air, water and food (*4, 7, 28*). This issue includes papers summarizing the methods used to estimate radiation exposure to individuals living near nuclear testing sites of the U.S. (Nevada, Marshall Islands) and the former Soviet Union (Semipalatinsk), the Mayak weapons production facility, and the Chornobyl nuclear reactor.

The Life Span Study (LSS) of atomic bomb survivors holds a unique place in the fields of physics, dosimetry, statistics, risk assessment and, of course, epidemiology. This study has been the greatest source of data and information on risks of acute whole-body exposure and has had the greatest impact on the development of radiation protection standards. The enormous and unique dosimetry effort has resulted in individual dose estimates for most organs and tissues for almost 90,000 survivors. Periodic updating and improvement of the dose estimates has helped make the LSS the ‘‘gold standard’’ for risk estimates (*29–36*) in radiation protection. A summary of the recently completed dosimetry system is presented in this issue.

Evaluation of certain biological end points that are quantitatively related to absorbed dose has contributed important independent estimates of radiation exposure in many epidemiological studies. When compared to dose estimates from analytical dose reconstruction, biological dosimetry may validate estimated doses (*17*) or give values inconsistent with estimated doses (*19, 20*). The disagreement between biological dosimetry and analytical dose reconstruction raises important questions about bias in reconstructed doses or problems of obtaining representative biological samples for the assays. The most widely used techniques for retrospective dosimetry—fluorescence *in situ* hybridization (FISH) of chromosomes, often called chromosome painting, glycophorin A somatic mutation assay (GPA), and electron paramagnetic resonance (EPR) measurements of teeth—are discussed in this issue.

In recent years, the epidemiology community has recognized that uncertainty in dose estimates can lead to misinterpretation of the dose response and can obscure a true dose–response relationship (*22*). This is particularly relevant to highly uncertain reconstructed doses, but it also applies to occupational and medical exposures based on measurements that are sometimes incorrectly assumed to be determined with high precision. Accounting for uncertainty in dose estimates, especially in studies of low doses, may be critical to drawing proper conclusions, computing appropriate confidence intervals and assessing risk, as well as ensuring credibility among our peers and the public. Analyses of the LSS data have been in the forefront in terms of accounting for uncertainty in the dose estimates (*37, 38*).

Many in the risk assessment field would agree that radiation dosimetry is the most advanced of all exposure assessment methods. Radiation physicists early on embraced the methods and necessity of error propagation. Their comfort with the mathematics of probability distributions, random number generation, and implementation of simulation models undoubtedly reflects their heritage in the Manhattan Project, where Monte Carlo methods were developed. The realization that dosimetric uncertainties are usually substantial, coupled with the development of computer simulation techniques, has made uncertainty less of a source of angst about the potential weakness of a study than it is a driving force behind innovation in analytical and statistical methods. A discussion is presented in this issue on how uncertainty can affect the crucial step in risk assessment—deriving the dose response—and how correcting for it can be tackled.

Combining the varied expertise of physicists, dosimetrists, statisticians and epidemiologists is a fairly recent phenomenon. It is one that we believe has many advantages and one we have implemented at the NCI, where these professionals work alongside one another as co-investigators on a variety of radiation-related epidemiological studies. This issue highlights the results of these interdisciplinary collaborations at NCI and elsewhere and makes them widely available. We hope that the readers of *Radiation Research* find this presentation to be useful and that it will stimulate further improvements in dosimetry and epidemiological studies.

REFERENCES

1. National Academy of Sciences, National Research Council, *Radiation Dose Reconstruction for Epidemiologic Uses*. National Academy Press, Washington, DC, 1995.
2. J. D. Boice, Jr., G. Engholm, R. A. Kleinerman, M. Blettner, M. Stovall, H. Lisco, W. C. Moloney, D. F. Austin, A. Bosch and B. MacMahon, Radiation dose and second cancer risk in patients treated for cancer of the cervix. *Radiat. Res.* **116**, 3–55 (1988).
3. M. Stovall, S. A. Smith and M. Rosenstein, Tissue doses from radiotherapy of cancer of the uterine cervix. *Med. Phys.* **16**, 726–733 (1989).
4. National Cancer Institute, *Estimated Exposures and Thyroid Doses Received by the American People from Iodine-131 in Fallout following Nevada Atmospheric Nuclear Bomb Tests: A Report of the National Cancer Institute*. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, Washington, DC, 1997.
5. A. Bouville and E. Ron, Thyroid cancer rates and 131-I doses from Nevada atmospheric nuclear bomb tests. *J. Natl. Cancer Inst.* **90**, 1654–1660 (1998).
6. A. Bouville, S. L. Simon, C. W. Miller, H. L. Beck, L. R. Anspaugh and B. G. Bennett, Estimates of doses from global fallout. *Health Phys.* **82**, 690–705 (2002).
7. K. Gordeev, I. Vasilenko, A. Lebedev, A. Bouville, N. Luckyanov, S. L. Simon, Y. Stepanov, S. Shinkarev and L. Anspaugh, Fallout from nuclear tests: Dosimetry in Kazakhstan. *Radiat. Environ. Biophys.* **41**, 61–67 (2002).
8. S. L. Simon and A. Bouville, Radiation doses to local populations near nuclear weapons testing sites worldwide. *Health Phys.* **82**, 706–725 (2002).
9. Y. I. Gavrilin, V. T. Khrouch, S. M. Shinkarev, N. A. Krysenko, A. M. Skryabin, A. Bouville and L. R. Anspaugh, Chernobyl accident: Reconstruction of thyroid dose for inhabitants of the Republic of Belarus. *Health Phys.* **76**, 105–119 (1999).
10. L. R. Anspaugh, S. L. Simon, K. I. Gordeev, I. A. Likhtarev and R. M. Maxwell, Movement of radionuclides in terrestrial ecosystems by physical processes. *Health Phys.* **82**, 669–679 (2002).
11. S. L. Simon, N. Luckyanov, A. Bouville, L. VanMiddlesworth and R. M. Weinstock, Transfer of ^{131}I into human breast milk and recommendations of transfer coefficient values for radiological dose assessments. *Health Phys.* **82**, 796–804 (2002).
12. J. H. Lubin, J. D. Boice and J. M. Samet, Errors in exposure assessment, statistical power, and interpretation of residential radon studies. *Radiat. Res.* **144**, 329–341 (1995).
13. Z. Y. Wang, J. H. Lubin, L. D. Wang, S. Z. Zhang, J. D. Boice, Jr., H. Z. Cui, S. R. Zhang, S. Conrath, Y. Xia and R. A. Kleinerman, Residential radon and lung cancer in a high exposure area in Gansu Province, China. *Am. J. Epidemiol.* **155**, 554–564 (2002).
14. M. C. R. Alavanja, J. H. Lubin, J. A. Mahaffey and R. C. Brownson, Residential radon exposure and risk of lung cancer in Missouri. *Am. J. Public Health* **89**, 1042–1048 (1999).
15. R. A. Kleinerman, L. G. Littlefield, S. G. Machado, M. Blettner, R. Tarone, L. J. Peters and J. D. Boice, Jr., Chromosome aberrations in peripheral lymphocytes and radiation dose to active bone marrow in patients treated for cancer of the cervix. *Radiat. Res.* **119**, 176–190 (1989).
16. R. A. Kleinerman, L. G. Littlefield, R. E. Tarone, A. M. Sayer, N. G. Hildreth, L. M. Pottern, S. G. Machado and J. D. Boice, Jr., Chromosome aberrations in relation to radiation dose following partial body exposures in three populations. *Radiat. Res.* **123**, 93–101 (1990).
17. L. G. Littlefield, R. A. Kleinerman, A. M. Sayer, R. Tarone and J. D. Boice, Jr., Chromosome aberrations in lymphocytes—biomonitors of radiation exposure. *Prog. Clin. Biol. Res.* **372**, 387–397 (1991).
18. W. L. Bigbee, R. H. Jensen, T. Veidebaum, M. Tekkel, M. Rahu, A. Stengrevics, A. Auvinen, T. Hakulinen, K. Servomaa and J. D. Boice, Jr., Biodosimetry of Chernobyl cleanup workers from Estonia and Latvia using the Glycophorin A *in vivo* somatic cell mutation assay. *Radiat. Res.* **147**, 215–224 (1997).
19. J. D. Tucker, E. J. Tawn, D. Holdsworth, S. Morris, R. Langlois, M. J. Ramsey, P. Kato, J. D. Boice, Jr., R. E. Tarone and R. H. Jensen, Biological dosimetry of radiation workers at the Sellafield Nuclear Facility. *Radiat. Res.* **148**, 216–226 (1997).
20. L. G. Littlefield, A. F. McFee, S. I. Salomaa, J. D. Tucker, P. D. Inskip, A. M. Sayer, C. Lindholm, S. Makinen, R. Mustonen and J. D. Boice, Jr., Do recorded doses overestimate true doses received by Chernobyl cleanup workers? Results of cytogenetic analyses of Estonian workers by fluorescence *in situ* hybridization. *Radiat. Res.* **150**, 237–249 (1998).
21. A. Romanyukha, M. Desrosiers, O. Sleptchonok, C. Land, N. Luckyanov and B. I. Gusev, EPR dose reconstruction of two Kazakh villages near the Semipalatinsk nuclear test site. *Appl. Magn. Reson.* **22**, 347–356 (2002).
22. E. Ron and F. O. Hoffman, Eds., *Uncertainties in Radiation Dosimetry and their Impact on Dose–Response Analyses*. NIH Publication no. 99-4541, U.S. Public Health Service, Washington, DC, 1999.
23. D. W. Schafer, J. H. Lubin, E. Ron, M. Stovall and R. J. Carroll, Thyroid cancer following scalp irradiation: A reanalysis accounting for uncertainty in dosimetry. *Biometrics* **57**, 689–697 (2001).
24. Z. A. Carr, R. A. Kleinerman, M. Stovall, R. M. Weinstock, M. L. Griem and C. E. Land, Malignant neoplasms after radiation therapy for peptic ulcer. *Radiat. Res.* **157**, 668–677 (2002).
25. E. S. Gilbert, M. Stovall, M. Gospodarowicz, F. E. Van Leeuwen, M. Andersson, B. Glimelius, T. Joensuu, C. F. Lynch, R. E. Curtis and L. B. Travis, Lung cancer after treatment for Hodgkin's disease: Focus on radiation effects. *Radiat. Res.* **159**, 161–173 (2003).
26. J. D. Boice, Jr., M. Blettner, R. A. Kleinerman, M. Stovall, W. C. Moloney, G. Engholm, D. F. Austin, A. Bosch, D. L. Cookfair and G. B. Hutchison, Radiation dose and leukemia risk in patients treated for cancer of the cervix. *J. Natl. Cancer Inst.* **79**, 1295–1311 (1987).
27. E. S. Gilbert, Studies of workers exposed to low doses of radiation. *Am. J. Epidemiol.* **153**, 319–322 (2001).
28. S. L. Simon, R. D. Lloyd, J. E. Till, H. A. Hawthorne, D. C. Gren, M. Rallison and W. Stevens, Development of a method to estimate dose from fallout radioiodine to persons in a thyroid cohort study. *Health Phys.* **59**, 669–691 (1990).
29. D. E. Thompson, K. Mabuchi, E. Ron, M. Soda, M. Tokunaga, S. Ochikubo, S. Sugimoto, T. Ikeda, M. Terasaki and D. L. Preston, Cancer incidence in atomic bomb survivors. Part II: Solid tumors, 1958–1987. *Radiat. Res.* **137** (Suppl.), S17–S67 (1994).
30. E. Ron, D. L. Preston, M. Kishikawa, T. Kobue, M. Iseki, S. Tokuoka, M. Tokunaga and K. Mabuchi, Skin tumor risk among atomic bomb survivors. *Cancer Causes Control* **9**, 393–401 (1998).
31. M. Tokunaga, C. E. Land, S. Tokuoka, I. Nishimori, M. Soda and S. Akiba, Incidence of female breast cancer among atomic bomb survivors, 1950–1985. *Radiat. Res.* **138**, 209–223 (1994).
32. D. A. Pierce, G. B. Sharp and K. Mabuchi, Joint effects of radiation and smoking on lung cancer risk among atomic bomb survivors. *Radiat. Res.* **159**, 511–520 (2003).
33. G. B. Sharp, T. Mizuno, J. B. Cologne, T. Fukuhara, S. Fujiwara, S. Tokuoka and K. Mabuchi, Hepatocellular carcinoma among atomic bomb survivors: Significant interaction of radiation with hepatitis C virus infections. *Int. J. Cancer* **103**, 531–537 (2003).
34. D. L. Preston, E. Ron, S. Yonehara, T. Kobuke, H. Fujii, M. Kishikawa, M. Tokunaga, S. Tokuoka and K. Mabuchi, Tumors of the nervous system and pituitary gland associated with atomic bomb radiation exposure. *J. Natl. Cancer Inst.* **94**, 1555–1563 (2002).
35. D. L. Preston, Y. Shimizu, D. A. Pierce, A. Suyama and K. Mabuchi, Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950–1997. *Radiat. Res.* **160**, 381–407 (2003).
36. C. E. Land, T. Saku, Y. Hayashi, O. Takahara, H. Matsuura, S. Tokuoka, M. Tokunaga and K. Mabuchi, Incidence of salivary gland tumors among atomic bomb survivors, 1950–1987. Evaluation of radiation-related risk. *Radiat. Res.* **146**, 28–36. (1996); Erratum, *Radiat. Res.* **146,** 356 (1996).
37. E. S. Gilbert, Some effects of random dose measurement errors on the analysis of atomic bomb survivor data. *Radiat. Res.* **98**, 591–605 (1982).
38. D. A. Pierce, D. O. Stram and M. Vaeth, Allowing for random errors in radiation dose estimates for the atomic bomb survivors. *Radiat. Res.* **123**, 275–284 (1990).